QUATERNARY SALT DERIVATIVES OF 1,4-DIPHENYLAZETIDIN-2-ONES

Field of the Invention

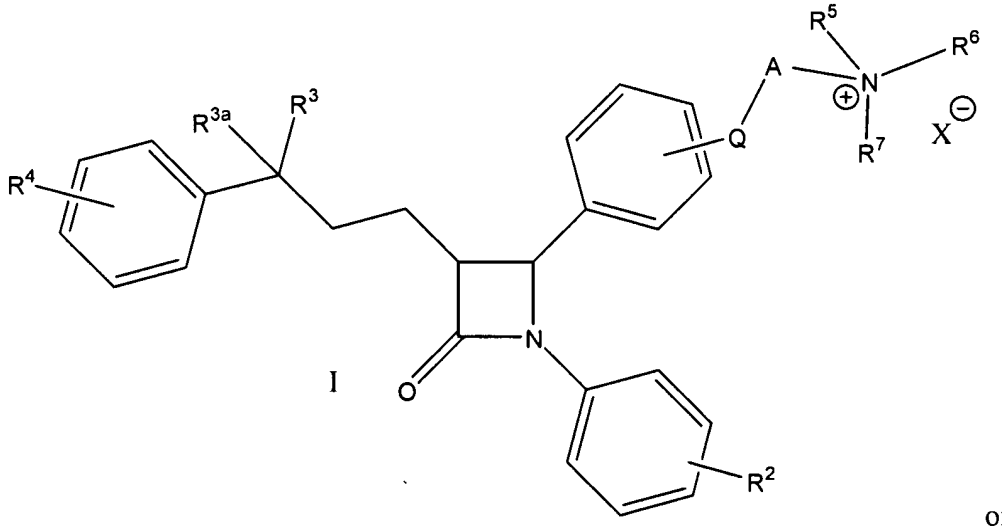
[001] The invention relates to a chemical genus of quaternary salt derivatives of 1,4-diphenylazetidin-2-ones useful for the treatment of hypercholesterolemia.

Background of the Invention

[002] 1,4-Diphenylazetidin-2-ones and their utility for treating disorders of lipid metabolism are described in US patent 6,498,156, USRE37721 and PCT application WO02/50027, the disclosures of which are incorporated herein by reference as they relate to utility.

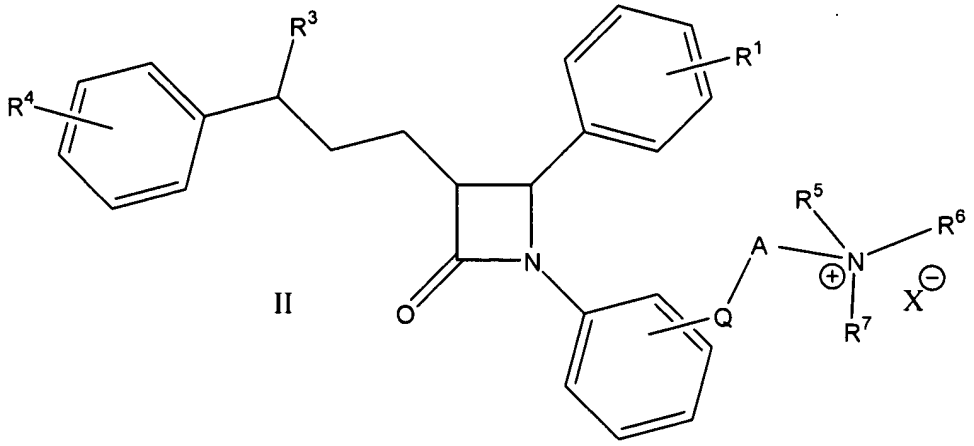
Summary of the Invention

[003] In one aspect the invention relates to compounds of the general formulae:



I

or



II

wherein

R^1 and R^2 are chosen from H, halogen, -OH, loweralkyl, -O-loweralkyl, -CN, -S-loweralkyl, amino, acyl, lower aminoalkyl, alkylsulfonyl, arylsulfonyl, a sugar, a glucuronide and a sugar carbamate;

R^3 is chosen from H, -OH, fluoro and -O-loweralkyl;

R^{3a} is chosen from H and fluoro, or R^{3a} and R^3 together are =O;

R^4 is chosen from H, halogen, -OH, loweralkyl, -O-loweralkyl, -CN, -S-loweralkyl, amino, acyl and lower aminoalkyl, alkylsulfonyl, arylsulfonyl;

Q is chosen from a direct bond, -O-, -S-, -NH-, $-CH_2O-$, $-CH_2NH-$, -C(=O)-, -CONH-, -NHCO-, -O(C=O)-, -(C=O)O-, -NHCONH-, -OCONH- and -NHCOO- ;

A is chosen from C_2 to C_{20} hydrocarbon, substituted alkyl of 2 to 20 carbons, substituted aryl, substituted arylalkyl, and oxaalkyl of four to fifty carbons; and, when Q is a direct bond, –C(=O) or –O(C=O)-, A may additionally be methylene;

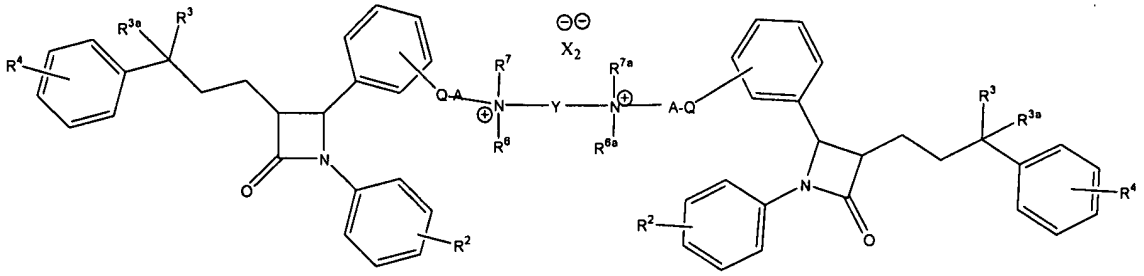
R^5 forms a five- to seven-membered ring with A or R^6;

R^6 is alkyl, forms a double bond with A or forms a five- to seven-membered ring with R^5;

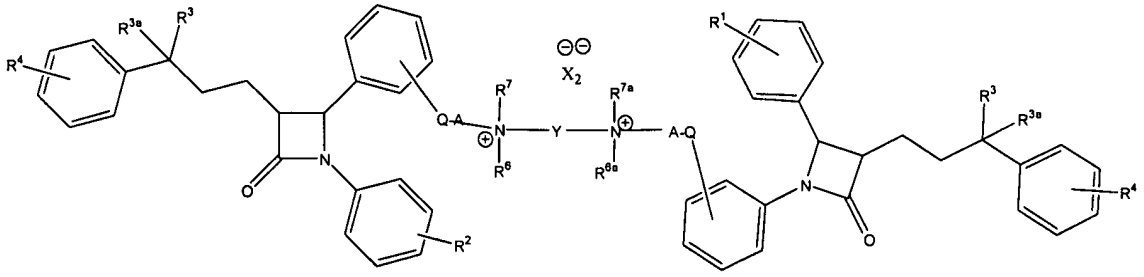
R^7 is alkyl or together with R^5 or R^6 forms a second five- to seven-membered ring; and when Q is not -O- or $-CH_2NH-$, R^5, may additionally be alkyl or aryl; and

X is an anion.

[004] In a second aspect the invention relates to compounds that may be thought of as isomeric "dimers" of the foregoing quats, namely isomers of formulae III, IV and V:

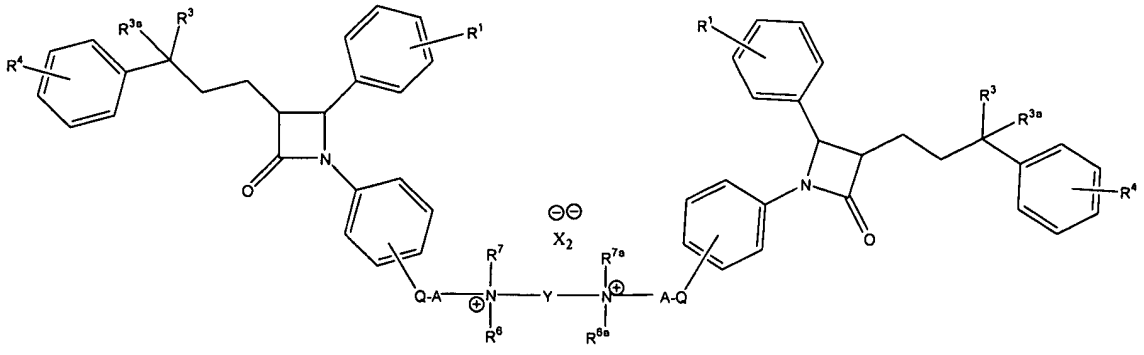


III



IV

and



V

in which the substituents are as defined before, and Y is chosen from C_2 to C_{20} hydrocarbon, substituted alkyl of 2 to 20 carbons, substituted arylalkyl and oxaalkyl of four to fifty carbons;
R^6 and R^{6a} are alkyl or together with Y form a first five- to seven-membered ring;
R^7 and R^{7a} are alkyl or together form a second five- to seven-membered ring; and
X_2 is either a dianion or two monoanions.

[005] In a third aspect the invention relates to pharmaceutical formulations comprising a pharmaceutically acceptable carrier and a compound as above having a pharmaceutically acceptable counter anion and, optionally additionally comprising one or more of (1) an inhibitor of cholesterol biosynthesis; (2) a cholesterol ester transfer protein (CETP) inhibitor; (3) a bile acid sequestrant; (4) a nicotinic acid or derivative thereof; (5) a peroxisome proliferator-activated receptor activator; (6) an acylcoenzyme A:cholesterol acyltransferase (ACAT) inhibitor; (7) an obesity control medication; and (8) a compound that normalizes lipid metabolism.

[006] In a fourth aspect, the invention relates to methods for treating a disorder of lipid metabolism, including hyperlipidemia, sitosterolemia and arteriosclerotic symptoms; inhibiting the absorption of cholesterol from the intestine; reducing the blood plasma or serum concentrations of LDL cholesterol; reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum; reducing blood plasma or serum concentrations of C-reactive protein (CRP), reducing blood plasma or serum concentrations of triglycerides; reducing blood plasma or serum concentrations of apolipoprotein B; increasing blood plasma or serum concentrations of high density lipoprotein (HDL) cholesterol; increasing the fecal excretion of cholesterol; treating a clinical condition for which a cholesterol absorption inhibitor is indicated and reducing the incidence of coronary heart disease-related events; reducing plasma or tissue concentration of at least one non-cholesterol sterol or 5α-stanol; treating or preventing vascular inflammation; preventing, treating, or ameliorating symptoms of Alzheimer's

Disease; regulating the production or level of at least one amyloid β peptide in bloodstream and/or brain of a subject; regulating the amount of ApoE isoform 4 in the bloodstream and/or brain; preventing and/or treating obesity; and preventing or decreasing the incidence of xanthomas. The methods comprise administering a compound described herein.

[007] In a fifth aspect, the invention relates to methods and compositions for prevention or treatment of a cholesterol-associated tumor. The methods comprise administering a therapeutically effective amount of a compound of the invention to a patient at risk of developing a cholesterol-associated tumor or already exhibiting a cholesterol-associated tumor. The method also includes coadministering a therapeutically effective amount of a compound of the invention and at least one other anticancer agent.

[008] In a sixth aspect, the invention relates to an article of manufacture comprising a container, instructions, and a pharmaceutical formulation as described above. The instructions are for the administration of the pharmaceutical formulation for a purpose chosen from: the prevention or treatment of a disorder of lipid metabolism; inhibiting the absorption of cholesterol from the intestine; reducing the plasma or tissue concentration of at least one non-cholesterol sterol or 5α-stanol; reducing the blood plasma or serum concentrations of LDL cholesterol; reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum; increasing the fecal excretion of cholesterol; reducing the incidence of coronary heart disease-related events; reducing blood plasma or serum concentrations of C-reactive protein (CRP); treating or preventing vascular inflammation; reducing blood plasma or serum concentrations of triglycerides; increasing blood plasma or serum concentrations of HDL cholesterol; reducing blood plasma or serum concentrations of apolipoprotein B; preventing, treating, or ameliorating symptoms of Alzheimer's Disease; regulating the production of amyloid β peptide; regulating the amount of ApoE isoform 4 in the bloodstream and/or brain; preventing and/or treating obesity; preventing or decreasing the incidence of xanthomas; and preventing or treating a cholesterol-associated tumor.

Detailed description of the Invention

[009] Compounds of the genera I-V above are inhibitors of cholesterol absorption from the intestine. As such they have utility in treating and preventing lipid disorders, such as hypercholesterolemia and hyperlipidemia. Because of their effect in lowering serum lipids, the compounds are useful in the treatment and prevention of atherosclerosis. The compounds can be used advantageously in combination with other hypolipidemic agents, including inhibitors of cholesterol biosynthesis, such as the HMG-CoA reductase inhibitors. Preferred HMG-CoA reductase inhibitors would include the "statins": lovastatin, simvastatin, pravastatin, rosuvastatin, mevastatin, atorvastatin, cerivastatin, pitavastatin and fluvastatin. A further listing of non-limiting examples of antihyperlipidemic agents that may be used in combination with the compounds of the present invention may be found in columns 5-6 of US patent 6,498,156, the disclosure of which is incorporated herein by reference.

[0010] As described above, the formulation may additionally contain at least one bile acid sequestrant. Sequestrants include cholestyramine, colestipol and colesevelam hydrochloride. The formulation may also contain a nicotinic acid or derivative thereof. Nicotinic acid derivatives include niceritrol, nicofuranose and acipimox. The formulation may also contain a peroxisome proliferator-activated receptor activator, which may be a fibric acid derivative. Fibric acids include fenofibrate, clofibrate, gemfibrozil, ciprofibrate, bezafibrate, clinofibrate, binifibrate and lifibrol. The formulation may also contain a CETP inhibitor. Examples of such are the compounds identified as JTT-705 in Nature. 406, (6792):203-7 (2000) and CP-529,414 (torcetrapib), described in US20030186952 and WO2000017164. Examples of CETP inhibitors are also found in Current Opinion in Investigational Drugs. 4(3):291-297 (2003). The formulation may also contain an ACAT inhibitor. Examples of such are the compounds identified as avasimibe in Current Opinion in Investigational Drugs. 3(9):291-297 (2003), and CL-277,082 in

Clin Pharmacol Ther. 48(2):189-94 (1990). The formulation may also contain an obesity control medication. Examples of obesity control medications include gut hormone fragment peptide YY_{3-36} (PYY_{3-36})(*N. Engl. J. Med.* 349:941, 2003; IKPEAPGE DASPEELNRY YASLRHYLNL VTRQRY) or a variant thereof, glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (focus vesiculosus), chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (teucrium chamaedrys), B-hydroxy-β-methylbutyrate, ATL-962 (Alizyme PLC), and T71 (Tularik, Inc.; Boulder CO), a ghrelin antagonist, Acomplia (rimonabant), AOD9604, alpha-lipoic acid (alpha-LA), and pyruvate.

[0011] The present invention is also directed to methods of prevention or treatment of a cholesterol-associated tumor in patients who are either at risk of developing a cholesterol-associated tumor or already exhibit a cholesterol-associated tumor. The tumor may be either a benign or a malignant tumor of the prostate, breast, endometrium or colon. The compounds of the invention may be co-administered with at least one other anticancer agent, which may be a steroidal antiandrogen, a non-steroidal antiandrogen, an estrogen, diethylstilbestrol, a conjugated estrogen, a selective estrogen receptor modulator (SERM), a taxane, or an LHRH analog. Tests showing the efficacy of the therapy and the rationale for combination therapy are presented in PCT application WO 2004/010948, the disclosure of which is incorporated herein by reference.

[0012] The compounds of the invention may reduce both cholesterol levels *in vivo* and epoxycholesterol formation and thereby inhibit initiation and progression of benign and malignant cholesterol-associated tumors or cholesterol-associated cell growth or cell-masses. Compositions disclosed herein, for example, are useful for the treatment and/or prevention of benign prostatic hypertrophy, as well as tumors associated with prostate,

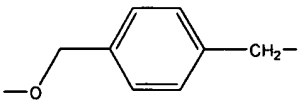
colon, endometrial, or breast tissues.

[0013] Compositions of the invention comprise an effective dose or a pharmaceutically effective amount or a therapeutically effective amount of a compound described above and may additionally comprise at least one other anticancer agent, for the treatment or prevention of benign prostatic hypertrophy or other cholesterol-related benign or malignant tumors, particularly those associated with prostate, breast, endometrial or colon tissues. Examples of agents for use in compositions and methods of the invention include steroidal or non steroidal antiandrogens such as finasteride (PROSCAR®), cyproterone acetate (CPA), flutamide (4'-nitro-3'-trifluorormethyl isobutyranilide), bicalutamide (CASODEX®), and nilutamide; estrogens, diethylstilbestrol (DES); conjugated estrogens (e.g., PREMARIN®); selective estrogen receptor modulator (SERM) compounds such as tamoxifen, raloxifene, droloxifene, idoxifene; taxanes such as paclitaxel (TAXOL®) and docetaxel (TAXOTERE®); and LHRH analogs such as goserelin acetate (ZOLADEX®), and leuprolide acetate (LUPRON®).

[0014] Methods of the invention parallel the compositions and formulations. The methods comprise co-administering to a patient in need of treatment a therapeutically effective amount of an azetidinone according to the invention and one or more of: (a) a steroidal or non steroidal antiandrogen; (b) an estrogen; (c) diethylstilbestrol (DES); (d) a conjugated estrogen; (e) a selective estrogen receptor modulator (SERM); (f) a taxane; and (g) an LHRH analog. The term "selective estrogen receptor modulator" includes both estrogen agonist and estrogen antagonists and refers to compounds that bind with the estrogen receptor, inhibit bone turnover and prevent bone loss. In particular, estrogen agonists are compounds capable of binding to the estrogen receptor sites in mammalian tissue and mimicking the actions of estrogen in that tissue. Estrogen antagonists are compounds capable of binding to the estrogen receptor sites in mammalian tissue and blocking the actions of estrogen in that tissue. Exemplary SERMs are: tamoxifen (U.S. Patent 4,536,516); 4-hydroxytamoxifen (U.S. Patent 4,623,660); raloxifene (U.S. Patent 4,418,068); idoxifene (U.S. Patent 4,839,155; and droloxifene. For the taxanes see U.S.

Patents 6,395,770; 6,380,405; and 6,239,167. Azetidinones of the invention may also be combined with a steroidal or non steroidal antiandrogen, as described above.

[0015] Certain compounds of the invention have the advantage that they suppress serum cholesterol and/or LDL levels but the compounds themselves are not appreciably absorbed into the mammalian circulation upon oral administration. As a result of the low-to-insignificant serum levels, fewer side-effects, such as drug-drug interactions, are observed.

[0016] Within the genus of the invention, subgenera include (a) those in which R^7 forms a second six-membered ring; (b) those in which -Q-A- is chosen from (C_2 to C_{20} hydrocarbon), -O-(C_2 to C_{20} hydrocarbon), -NH(C_2 to C_{20} hydrocarbon), -NHCO(C_2 to C_{20} hydrocarbon) and oxaalkyl of four to fifty carbons; (c) those in which R^1 and R^2 are H, halogen, -OH, or methoxy; R^3 is -OH; and R^4 is fluoro; (d) those in which R^1 and R^2 are chosen from a sugar, a glucuronide and a sugar carbamate; R^3 is -OH; and R^4 is fluoro; and (e) those in which -Q-A- is 

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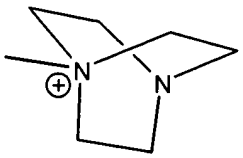
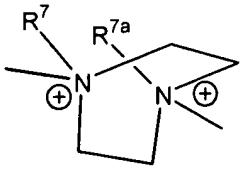
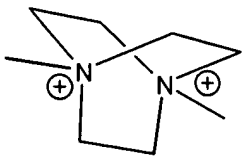
[0017] One preferred subgenus of genera I and II is that in which R^5,R^6 and R^7 taken together form a diazabicyclooctane quat:



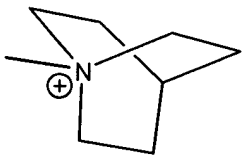
[0018] A subgenus of genera III, IV and V is that in which R^6 and R^{6a} taken together with Y form a dialkyl piperazinium bisquat:



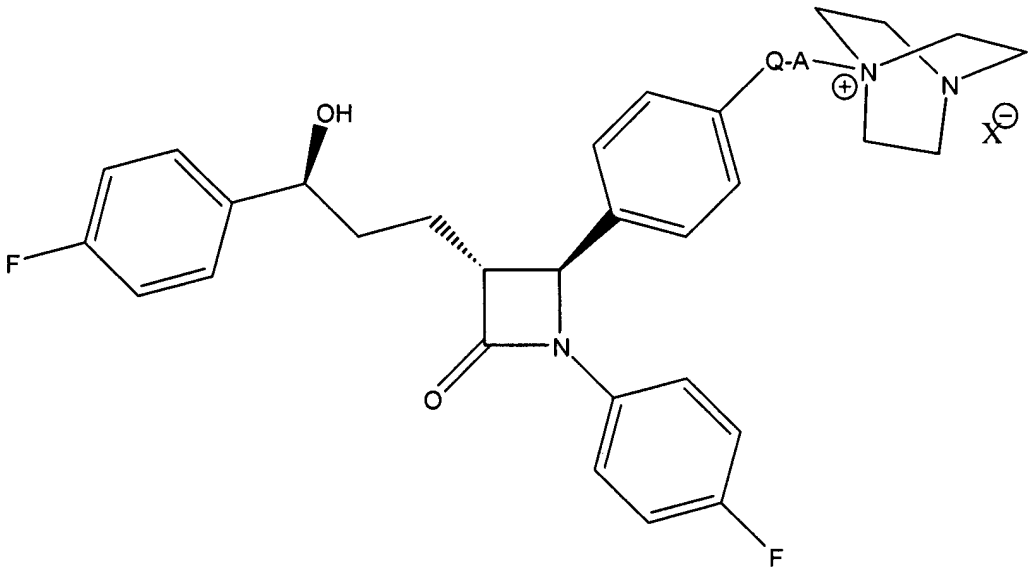
[0019] A further subgenus of genera III, IV and V related to the dialkyl piperazinium bisquats is that in which R^6, R^{6a}, R^7 and R7a taken together with Y form a diazabicyclooctane bisquat:

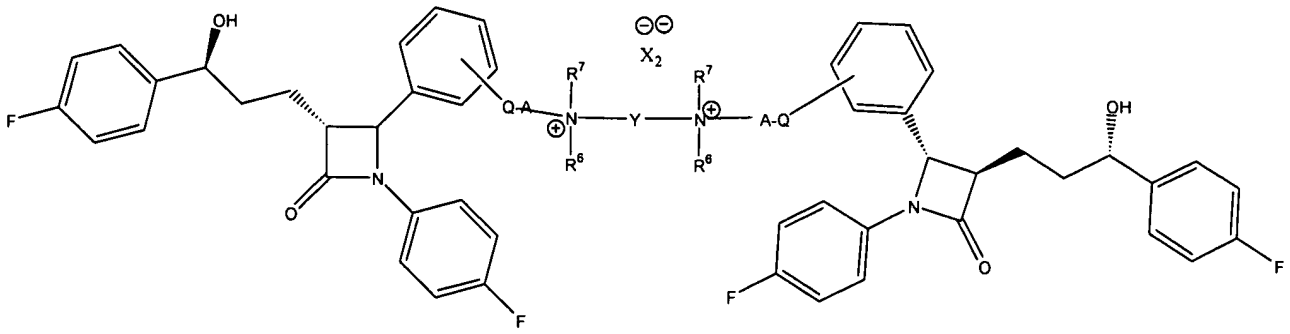


[0020] Another preferred subgenus of genera I and II is that in which R^5,R^6 and R^7 taken together form a quinuclidinium quat:

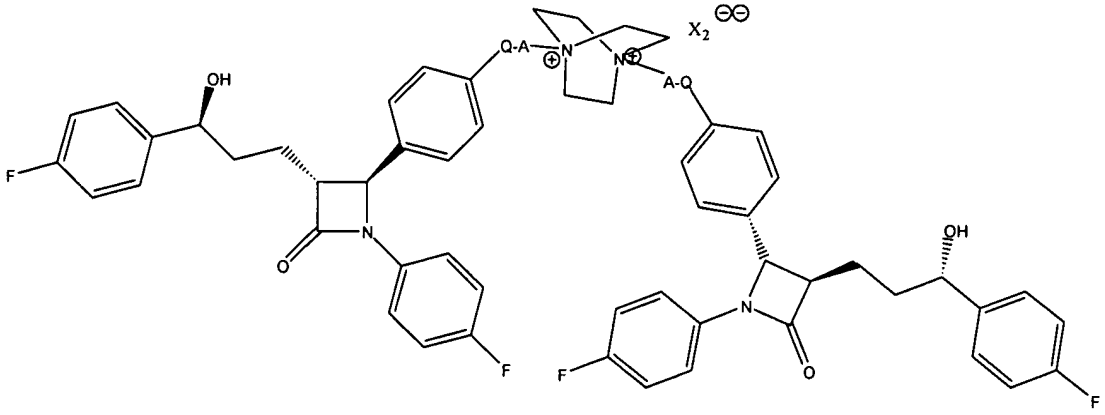


[0021] Exemplary compounds of the invention include:





and



[0022] Other subgenera of genera I and II are those in which R^5 forms a five- to seven-membered ring with A, R^6 forms a double bond with A and R^7 is alkyl.

[0023] The compounds of the invention are quaternary salts, i.e. cationic species. Therefore they will always be presented as salts, and the term "pharmaceutically acceptable salt" refers to salts whose counter ion (anion) derives from pharmaceutically acceptable non-toxic acids including inorganic acids, organic acids and water (which formally furnishes the hydroxide anion). Suitable pharmaceutically acceptable anions for the compounds of the present invention include hydroxide, acetate, benzenesulfonate (besylate), benzoate, bicarbonate, bisulfate, carbonate, camphorsulfonate, citrate, ethanesulfonate, fumarate, gluconate, glutamate, glycolate, bromide, chloride, isethionate, lactate, maleate, malate, mandelate, methanesulfonate, mucate, nitrate, pamoate,

pantothenate, phosphate, succinate, sulfate, tartrate, trifluoroacetate, p-toluenesulfonate, acetamidobenzoate, adipate, alginate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, calcium edetate, camphorate, camsylate, caprate, caproate, caprylate, cinnamate, cyclamate, dichloroacetate, edetate (EDTA), edisylate, embonate, estolate, esylate, fluoride, formate, gentisate, gluceptate, glucuronate, glycerophosphate, glycolate, glycollylarsanilate, hexylresorcinate, hippurate, hydroxynaphthoate, iodide, lactobionate, malonate, mesylate, napadisylate, napsylate, nicotinate, oleate, orotate, oxalate, oxoglutarate, palmitate, pectinate, pectinate polymer, phenylethylbarbiturate, picrate, pidolate, propionate, rhodanide, salicylate, sebacate, stearate, tannate, theoclate, tosylate and the like. The desired salt may be obtained by ion exchange of whatever counter ion is obtained in the synthesis of the quat. These methods are well known to persons of skill. Although pharmaceutically acceptable counter ions will be preferred for preparing pharmaceutical formulations, other anions are quite acceptable as synthetic intermediates. Thus X may be pharmaceutically undesirable anions, such as iodide, oxalate, trifluoromethanesulfonate and the like, when such salts are chemical intermediates. When the compounds of the invention are bisquats, one may employ as counter ions either two monoanionic species (e.g. Cl_2) or a single dianionic species (e.g. fumarate). Similarly, one could employ oligoanionic species and make salts having appropriate ratios of quat to counterion, such as $(quat)_3$ citrates. These would be obvious equivalents.

Definitions

[0024] Throughout this specification the terms and substituents retain their definitions.

[0025] Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. Lower alkyl refers to alkyl groups of from 1 to 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-and t-butyl and the like. Preferred alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 8 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl

and the like.

[0026] C_1 to C_{20} Hydrocarbon includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl.

[0027] Alkoxy or alkoxyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to four carbons.

[0028] Oxaalkyl refers to alkyl residues in which one or more carbons (and their associated hydrogens) have been replaced by oxygen. Examples include methoxypropoxy, 3,6,9-trioxadecyl and the like. The term oxaalkyl is intended as it is understood in the art [see Naming and Indexing of Chemical Substances for Chemical Abstracts, published by the American Chemical Society, ¶196, but without the restriction of ¶127(a)], i.e. it refers to compounds in which the oxygen is bonded via a single bond to its adjacent atoms (forming ether bonds). Similarly, thiaalkyl and azaalkyl refer to alkyl residues in which one or more carbons have been replaced by sulfur or nitrogen, respectively. Examples include ethylaminoethyl and methylthiopropyl.

[0029] Acyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

[0030] Aryl and heteroaryl mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0-3 heteroatoms selected from O, N, or S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S; or a tricyclic 13- or 14-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S. Aromatic 6- to 14-membered carbocyclic rings include, *e.g.,* benzene, naphthalene, indane, tetralin, and fluorene and the 5- to 10-membered aromatic heterocyclic rings include, *e.g.*, imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

[0031] Arylalkyl means an alkyl residue attached to an aryl ring. Examples are benzyl, phenethyl and the like.

[0032] Substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein up to three H atoms in each residue are replaced with halogen, haloalkyl, hydroxy, loweralkoxy, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide, sulfone, acylamino, amidino, phenyl, benzyl, heteroaryl, phenoxy, benzyloxy, or heteroaryloxy.

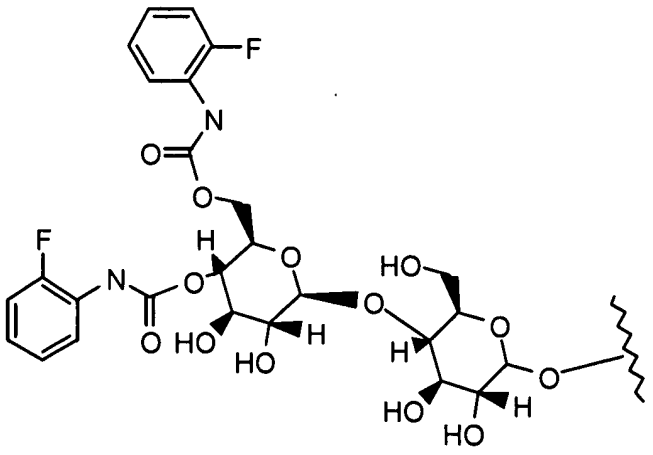
[0033] The term "halogen" means fluorine, chlorine, bromine or iodine.

[0034] The term "sugar" is used in its normal sense, as defined in Hawley's Condensed Chemical Dictionary, 12th Edition, Richard J. Lewis, Sr.; Van Nostrand Reinhold Co. New York. It encompasses any carbohydrate comprised of one or two saccharose groups. The monosaccharide sugars (often called simple sugars) are composed of chains of 2-7 carbon atoms. One of the carbons carries aldehydic or ketonic oxygen, which may be combined in acetal or ketal forms. The remaining carbons usually have hydrogen atoms and hydroxyl groups. Among monosaccharides which would be considered within the term "sugars" as intended in this application, are arabinose, ribose, xylose, ribulose,

xylulose, deoxyribose, galactose, glucose, mannose, fructose, sorbose, tagatose, fucose, quinovose, rhamnose, manno-heptulose and sedoheptulose. Among the disaccharides are sucrose, lactose, maltose, and cellobiose. Unless specifically modified, the general term "sugar" refers to both D-sugars and L-sugars.

[0035] The term "glucuronide" is also used in its normal sense to refer to a glycoside of glucuronic acid.

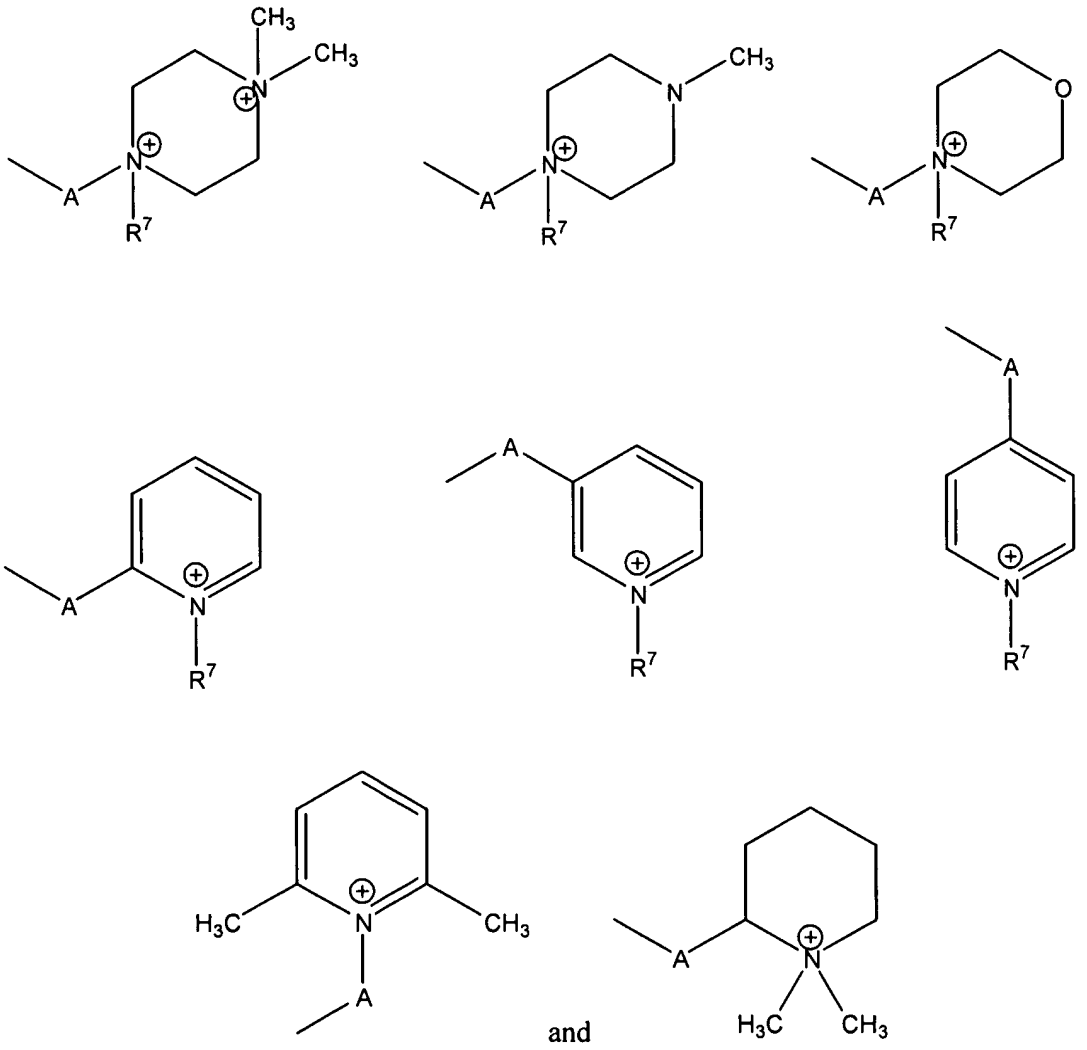
[0036] The term "sugar carbamate" refers to mono-, di- and oligosaccharides in which one or more hydroxyls have been derivatized as carbamates, particularly as phenyl carbamates and substituted phenyl carbamates. [See Detmers et al. Biochim Biophys. Acta 1486, 243-252 (2000), which is incorporated herein by reference.] A preferred sugarcarbamate is:



[0037] The term "prodrug" refers to a compound that is made more active *in vivo*. Since the compounds of the invention are minimally absorbed into the systemic circulation, activation *in vivo* may come about by chemical action or through the intermediacy of enzymes and microflora in the GI tract.

[0038] In the characterization of the variables, it is recited that R^5 may form a five- to seven-membered ring with A or R^6; that R^6 may form a double bond with A or may form a five- to seven-membered ring with R^5; and that R^7 may form a second five- to seven-

membered ring. It is intended that these rings may exhibit various degrees of unsaturation (from fully saturated to aromatic), may include heteroatoms and may be substituted with lower alkyl or alkoxy. Examples of the -A-$NR^5R^6R^7$ residue that fall within this subgenus include:



[0039] It will be recognized that the compounds of this invention can exist in radiolabeled form, i.e., the compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine, and chlorine

include ^{3}H, ^{14}C, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds that contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of this invention. Tritiated, i.e. ^{3}H, and carbon-14, i.e., ^{14}C, radioisotopes are particularly preferred for their ease in preparation and detectability. Radiolabeled compounds of Formulas I-VII of this invention and prodrugs thereof can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabeled compounds can be prepared by carrying out the procedures disclosed in the Examples and Schemes by substituting a readily available radiolabeled reagent for a non-radiolabeled reagent.

[0040] The terms "methods of treating or preventing" mean amelioration, prevention or relief from the symptoms and/or effects associated with lipid disorders. The term "preventing" as used herein refers to administering a medicament beforehand to forestall or obtund an acute episode. The person of ordinary skill in the medical art (to which the present method claims are directed) recognizes that the term "prevent" is not an absolute term. In the medical art it is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or seriousness of a condition, and this is the sense intended in applicants' claims. As used herein, reference to "treatment" of a patient is intended to include prophylaxis. Throughout this application, various references are referred to within parentheses or square brackets. The disclosures of these publications in their entireties are hereby incorporated by reference as if written herein.

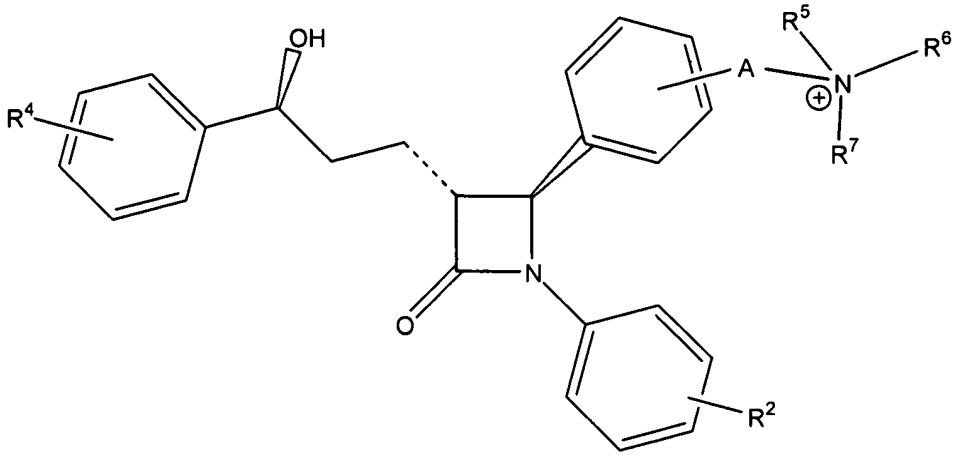
[0041] The term "mammal" is used in its dictionary sense. The term "mammal" includes, for example, mice, hamsters, rats, cows, sheep, pigs, goats, and horses, monkeys, dogs (e.g., *Canis familiaris*), cats, rabbits, guinea pigs, and primates, including humans.

[0042] The compounds may be used to treat or prevent vascular inflammation, as described in US published application 20030119757; to prevent, treat, or ameliorate symptoms of Alzheimer's Disease and to regulate the production or level of amyloid β

peptide and ApoE isoform 4, as described in US patent 6,080,778 and US published application 20030013699; and to prevent or decrease the incidence of xanthomas, as described in US published application 20030119809. The disclosures of all are incorporated herein by reference as they relate to utility.

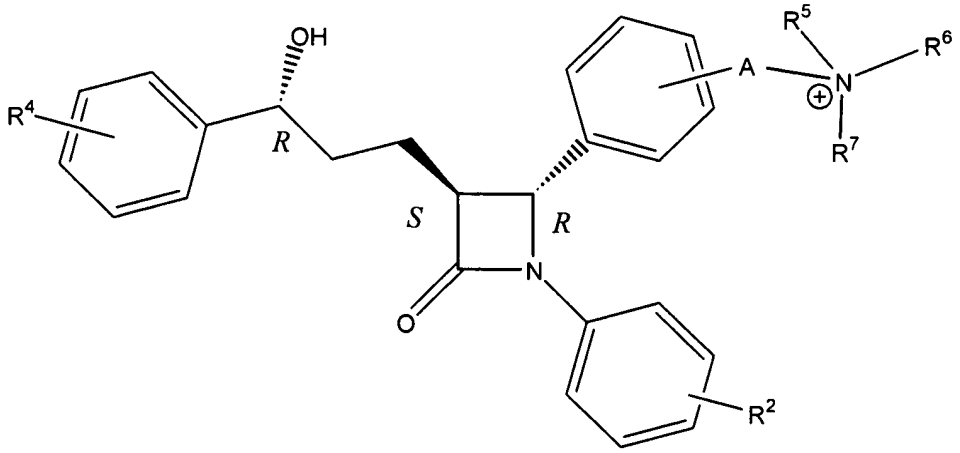
[0043] The compounds described herein contain two or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0044] The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr J. Chem. Ed. 62, 114-120 (1985): solid and broken wedges are used to denote the absolute configuration of a chiral element; wavy lines and single thin lines indicate disavowal of any stereochemical implication which the bond it represents could generate; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration. Thus, the formula X is intended to encompass both of the pure enantiomers of that pair:

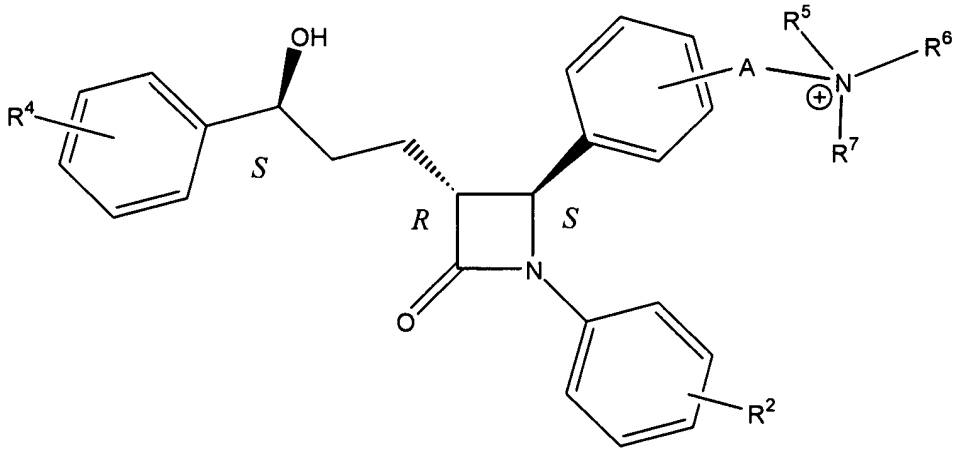


X

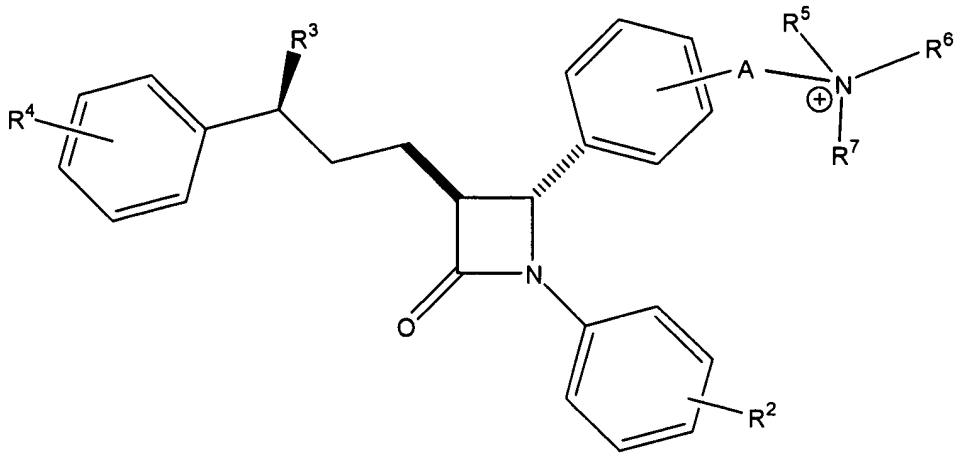
Means either pure R,S,R:



or pure S,R,S:



whereas



refers to a racemic mixture of S,R,S and S,S,R, i.e. having a trans relative configuration on the beta lactam ring.

[0045] The term "enantiomeric excess" is well known in the art and is defined for a resolution of ab ? a + b as

$$ee_a = \left(\frac{conc.\ of\ a - conc.\ of\ b}{conc.\ of\ a + conc.\ of\ b} \right) x\ 100$$

[0046] The term "enantiomeric excess" is related to the older term "optical purity" in that both are measures of the same phenomenon. The value of ee will be a number from 0 to 100, zero being racemic and 100 being pure, single enantiomer. A compound which in the past might have been called 98% optically pure is now more precisely described as 96% ee; in other words, a 90% ee reflects the presence of 95% of one enantiomer and 5% of the other in the material in question.

[0047] The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis, trans*, or a mixture of the two in any proportion.

[0048] Terminology related to "protecting", "deprotecting" and "protected" functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes which involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group which is used to mask a functionality during a process step in which it would otherwise react, but in which reaction is undesirable. The protecting group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or "deprotection" occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is in the processes of the invention, the person of ordinary skill can readily envision those groups that would be suitable as "protecting groups". Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as Protective Groups in Organic Synthesis by T.W.Greene [John Wiley & Sons, New York, 1991], which is incorporated herein by reference. Particular attention is drawn to the chapters entitled "Protection for the Hydroxyl Group, Including 1,2- and 1,3-Diols" (pages 10-86).

[0049] The abbreviations Me, Et, Ph, Tf, Ts and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, toluensulfonyl and methanesulfonyl respectively. A comprehensive list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of Organic Chemistry. The list, which is typically presented in a table entitled "Standard List of Abbreviations" is incorporated herein by reference.

[0050] While it may be possible for the compounds of formula (I) to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable"

in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0051] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration. The most suitable route may depend upon the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0052] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0053] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained,

delayed or controlled release of the active ingredient therein.

[0054] The pharmaceutical compositions may include a "pharmaceutically acceptable inert carrier", and this expression is intended to include one or more inert excipients, which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques, "Pharmaceutically acceptable carrier" also encompasses controlled release means.

[0055] Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must, of course, be compatible with the compound of the invention to insure the stability of the formulation.

[0056] Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to:

[0057] BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch (*e.g.*, STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof;

[0058] FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder),

microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof;

[0059] DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate , microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, or mixtures thereof;

[0060] LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil *e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof;

[0061] ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof;

[0062] ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof; and

[0063] COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose,

titanium dioxide, carnuba wax, microcrystalline wax, or mixtures thereof.

[0064] The dose range for adult humans is generally from 0.005 mg to 10 g/day orally. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10mg to 200mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

[0065] Combination therapy can be achieved by administering two or more agents, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so. Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

[0066] In Vivo Assay of Hypolipidemic Agents using the Rat Cholesterol Absorption Model. This model is based on models described by Burnett et al (2002), Bioorg Med Chem Lett. 2002 Feb 11;12(3):315-8 and J Lipid Res. 1999 Oct;40(10):1747-57. Female Sprague-Dawley rats weighing 150-250g are separated into groups of 3-6 and fasted overnight. The animals (4-6/group) are dosed perorally with 300μL test compounds in olive oil or suitable vehicle. Thirty minutes later, 3-5 microCuries ^{3}H-cholesterol per rat are delivered perorally in 300 μL olive oil . After three hours, 200 μL serum is collected, vortexed with scintillation fluid, and measured for radioactivity in a scintillation counter. Percent inhibition is defined as $100*(1-C_{test}/C_{ctrl})$, where C_{test} and C_{ctrl} refer to ^{3}H levels in serum for the test compound and for the vehicle only control, respectively. Percent inhibition values are reported for a fixed dose. The ED_{50} is the dose at which the half-maximal effect on serum ^{3}H levels is observed for a given test compound.

[0067] In Vivo Assay of Hypolipidemic Agents using the Mouse Cholesterol Absorption Model. Female CD-1 mice weighing 20-30g are separated into groups of 3-8 and fasted overnight. The animals (3-8/group) are dosed perorally with 200μL test compound in olive oil or suitable vehicle. Thirty minutes later, 3-5 microCuries ^{3}H-cholesterol per mouse are delivered perorally in 200 μL olive oil. After three hours, 100 μL serum is collected, vortexed with scintillation fluid, and measured for radioactivity in a scintillation counter. Percent inhibition and ED_{50} are defined as in the Rat Cholesterol Absorption Model above.

[0068] In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster: Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by intramuscular (IM)

injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis is conducted as per published procedures [Schnitzer-Polokoff, R., et al, *Comp. Biochem. Physiol.*, 99A, 4, 665-670 (1991)] and data are reported as percent reduction of lipid versus control.

[0069] In Vivo Assay of Hypolipidemic Agents using the Hamster Acute Cholesterol Absorption Model. Male Syrian Hamsters weighing 120g are separated into groups of 3-6 and fasted overnight. The animals (3-6/group) are dosed perorally with 200μL test compound in olive oil or suitable vehicle. Thirty minutes later, 3-5 microCuries ^{3}H-cholesterol per hamster are delivered perorally in 200 μL olive oil. After three hours, 100-200 μL serum is collected, vortexed with scintillation fluid, and measured for radioactivity in a scintillation counter. Percent inhibition and ED_{50} are defined as in the Rat Cholesterol Absorption Model above.

[0070] The bioabsorption of the compounds herein described may be examined using the Caco-2 cell monolayer model of Hilger *et al.* [Pharm. Res. 7, 902 (1990)].

[0071] To study the pharmacokinetics of compounds, bioavailability studies are carried out in rats. Compounds are prepared in suitable formulations: 5% ethanol in olive oil for oral administration and 2% DMSO: 20% cyclodextrins in H_2O for intravenous administration. Compounds are administered intravenously via tail vein injection and orally by gavage to independent groups of CD rats (200-250g). Serum is collected at various time points and assayed for the presence of compounds using an LC/MS/MS detection method. Samples are diluted 15-fold in 30% acetonitrile in water, then injected (35 μL) into a 3.2 ml/min flow of 5% methanol in water onto a sample extraction cartridge (Waters Oasis HLB Direct Connect), washed for 30 seconds, then loaded onto a reverse phase HPLC column (Thermo Electron Betasil C18 Pioneer 50 x 2.1 mm, 5 um particle size). Samples are eluted from the reverse phase HPLC column with a gradient: (Mobile Phase A: 5 mM ammonium acetate in dH_2O, Mobile Phase B: 20% methanol in

acetonitrile; 40% B ramping to 95% B over 4 minutes, and holding for 3 minutes, then returning to initial conditions to re-equilibrate the column for 1 min, all at a flow rate of 0.3 ml/min.). A Micromass Quattro Micro (Waters Corp.; Milford, MA) triple quadrupole mass spectrometer operated in MRM mode is used for detection. Concentrations are calculated based on standard concentration curves of compounds. MassLynx software (Waters, Corp.; Milford, MA) is used to calculate the absolute concentration of test compound in each serum sample. A concentration versus time plot is generated from the data in Microsoft Excel, Summit Software PK Solutions 2.0 or GraphPad Prism (GraphPad Software, Inc., San Diego, CA) to generate pharmacokinetic curves. An area under the curve (AUC_n, n = length of experiment in minutes or hours) is calculated from the concentration *vs.* time data by the software using the trapezoid method for both the orally and intravenously dosed animals. Oral Bioavailability (F) over the length of the experiment is calculated using the equation:

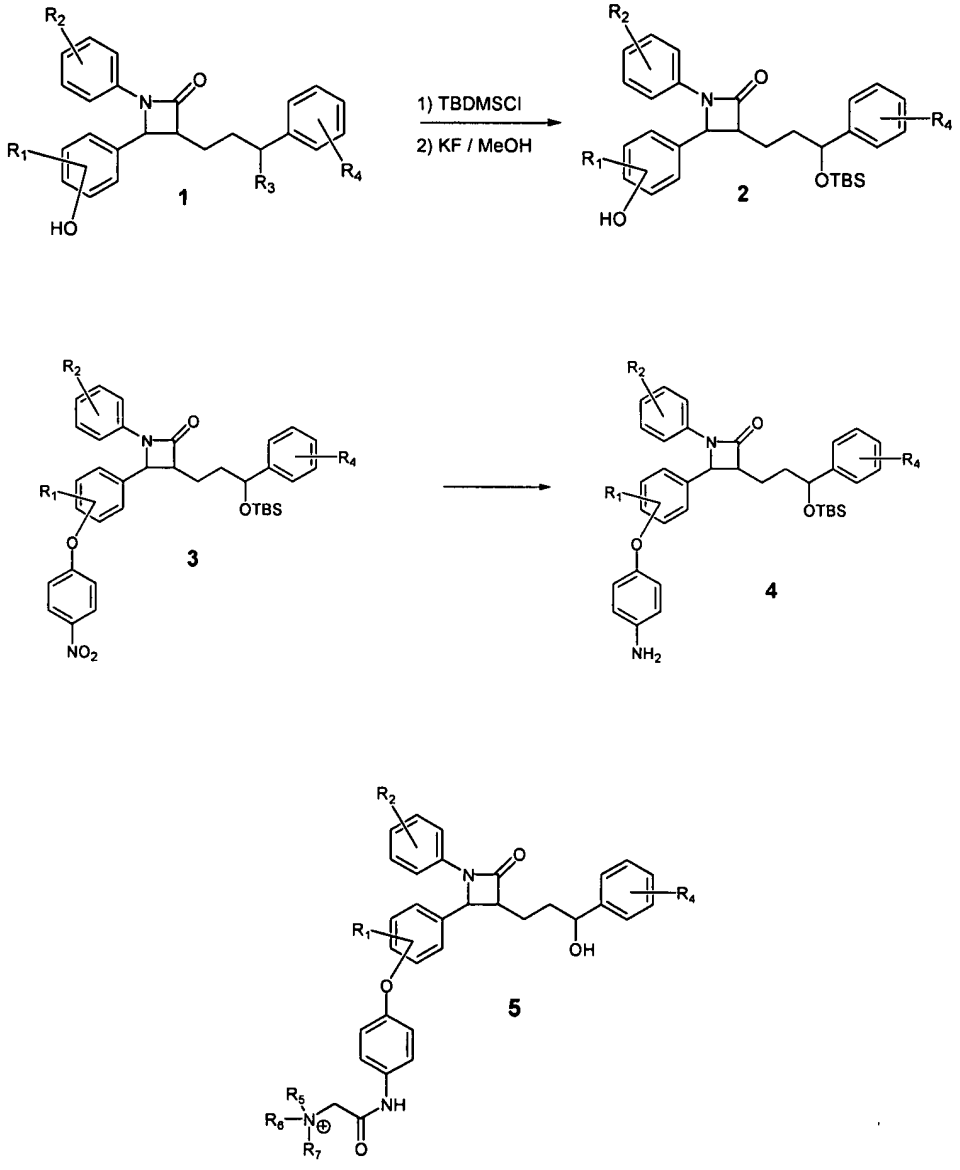
$$F = (AUC_{oral} * Dose_{i.v.}) / (AUC_{i.v.} * Dose_{oral})$$

[0072] In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are in themselves known, but are not mentioned here.

[0073] The starting materials, in the case of suitably substituted azetidinones, may be obtained by the methods described in WO 02/50027, WO 97/16424, WO 95/26334, WO 95/08532 and WO 93/02048, the disclosures of which are incorporated herein by reference.

[0074] Processes for obtaining the compounds of the invention are presented below.

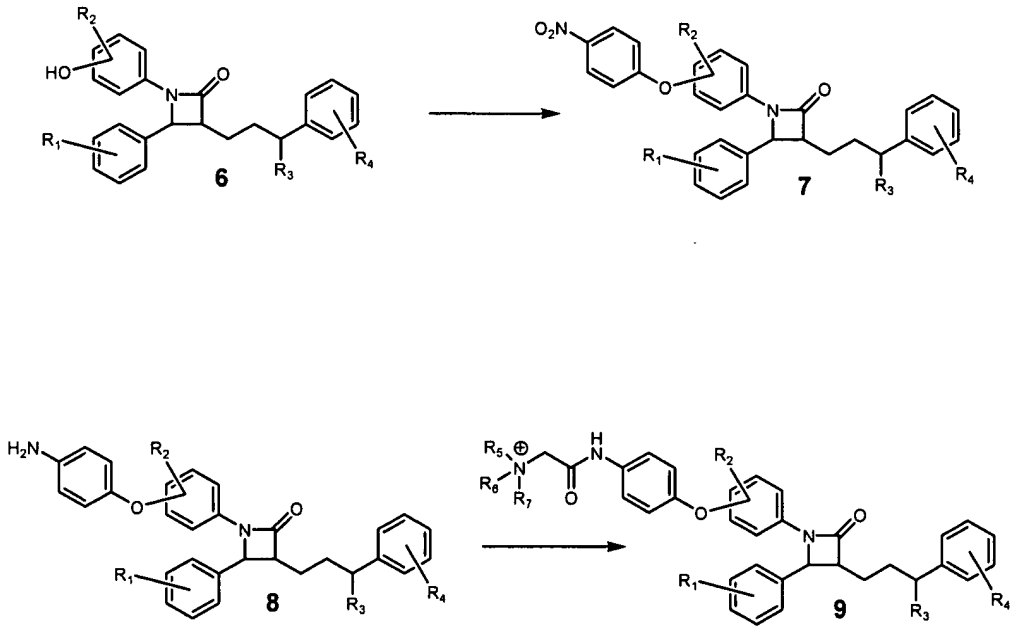
[0075] Scheme I



The method for the preparation of cholesterol absorption inhibitors illustrated in Scheme I begins with the double protection of the phenolic and benzylic hydroxyl moieties as *tert*-

butyldimethylsilyl ethers (TBS). The *bis*-TBS ether is then subjected to treatment with methanolic potassium fluoride, which effects a selective deprotection of the phenol hydroxyl to afford compounds of the general formula **2**. Treatment of the protected phenols (**2**) with 4-fluoronitrobenzene in the presence of base provided the nitrophenyl ether derivatives **3** which were converted to the corresponding anilines (**4**) upon catalytic hydrogenation. Acylation of aniline **4** with chloro or bromoacetic acid gave the corresponding alpha-halo acetyl derivatives, which were condensed with amines to afford the ammonium salts that were deprotected to the cholesterol absorption inhibitors **5**. Alternatively, the anilines **4** could be condensed with *alpha*-ammonium salts of acetic acid and then deprotected to give the desired inhibitors **5**.

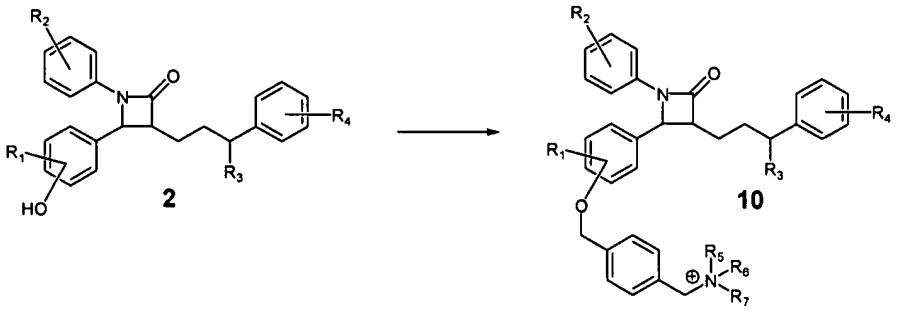
[0076] Scheme II



Scheme II illustrates the method that was used for the preparation of cholesterol absorption inhibitors that are isomeric with the derivatives described in Scheme I. The mono-protected phenol **6** was condensed with 4-fluoronitrobenzene to provide phenyl

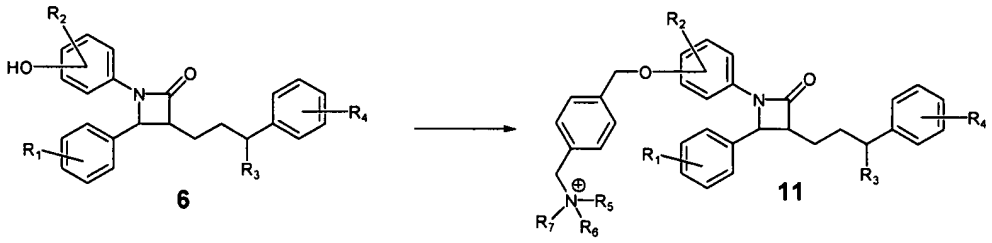
ethers 7. Catalytic hydrogenation of 7 afforded the corresponding anilines 8 which were converted into the cholesterol absorption inhibitors 9 as described in Scheme I.

[0077] Scheme III



Scheme III illustrates the preparation of cholesterol absorption inhibitors of the type exemplified by quaternary ammonium salt **10**. The synthesis begins with the unprotected phenols of the formula **1**. Treatment of **1** with α,α'-dibromo-*p*-xylene followed by condensation with a tertiary amine afforded compounds of the formula **10**. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **10** wherein R_3 = OH.

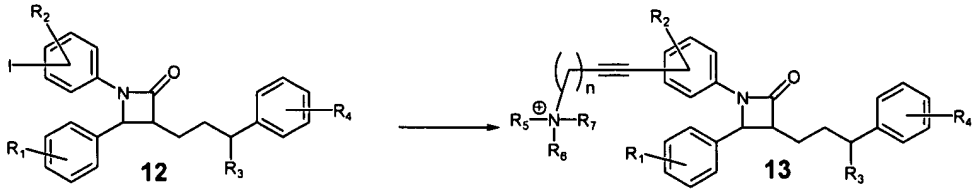
[0078] Scheme IV



Scheme IV illustrates the preparation of cholesterol absorption inhibitors of the type exemplified by quaternary ammonium salt **11**. The synthesis begins with phenols of the formula **6**. Treatment of **6** with α,α'-dibromo-*p*-xylene followed by condensation with a tertiary amine afforded compounds of the formula **11**. Deprotection of the benzylic TBS

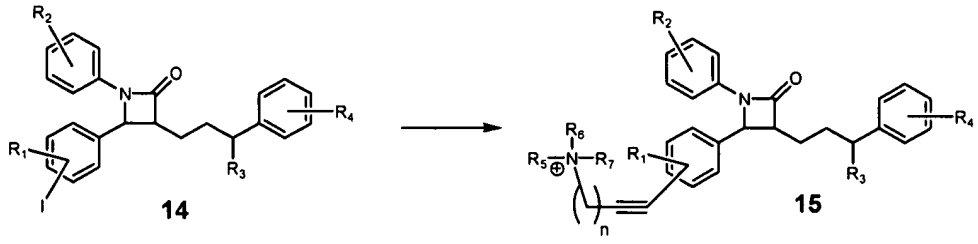
ether (if present) then affords the desired cholesterol absorption inhibitors **11** wherein R_3 = OH.

[0079] Scheme V



Scheme V illustrates the method that was employed for the preparation of cholesterol absorption inhibitors of the type exemplified by structure **13**. The synthesis commences with condensation of an acetylenic derivative with an iodo substituted derivative **12** under Sonogoshira reaction conditions. The acetylene-substituted products were then converted into the corresponding ammonium salts (**13**) by quaternization of the appropriate bromide or sulfonate ester derivatives with an appropriate amine. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **13** wherein R_3 = OH.

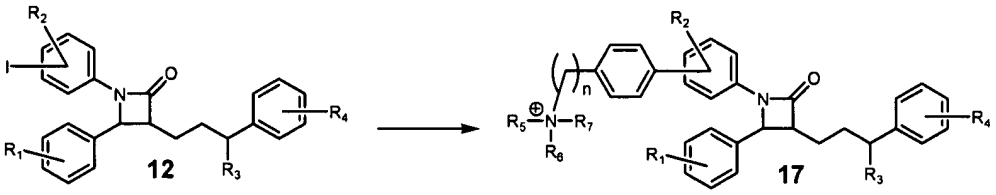
[0080] Scheme VI



Scheme VI illustrates the method that was employed for the preparation of cholesterol absorption inhibitors of the type exemplified by structure **15**. The synthesis commences with condensation of an acetylenic derivative with an iodo substituted derivative **14** under Sonogoshira reaction conditions. The acetylene-substituted products were then converted

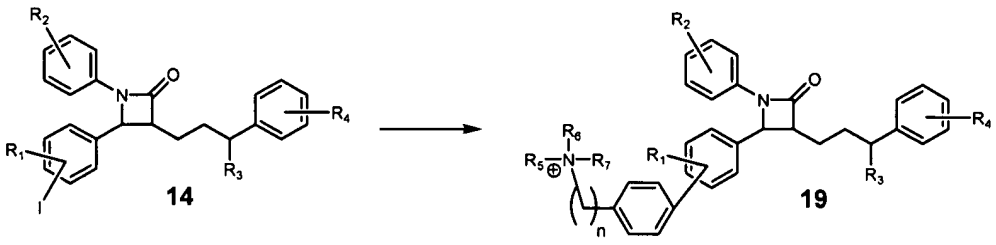
into the corresponding ammonium salts (**15**) by quaternization of the appropriate bromide or sulfonate ester derivatives with an appropriate amine. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **15** wherein R_3 = OH.

[0081] Scheme VII



Scheme VII illustrates the method utilized for the preparation of cholesterol absorption inhibitors of the type exemplified by structure **17**. The sequence commences by coupling the aromatic iodide **12** with an appropriately substituted aryl or alkyl boronic acid by Suzuki reaction conditions. Conversion of the coupling product to the desired ammonium salts **17** was then accomplished by preparation of the corresponding aryl bromide or sulfonate ester derivatives followed by quaternization with an appropriate amine. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **17** wherein R_3 = OH.

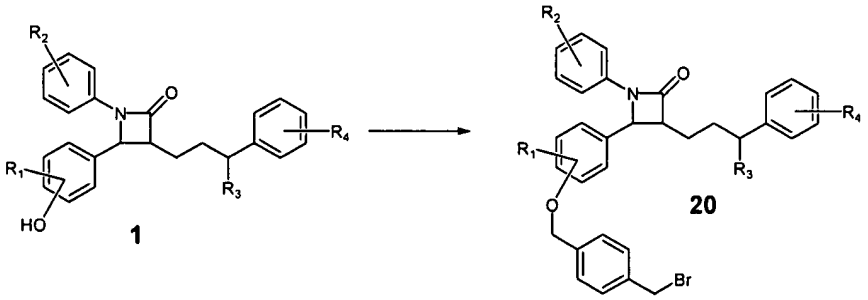
[0082] Scheme VIII

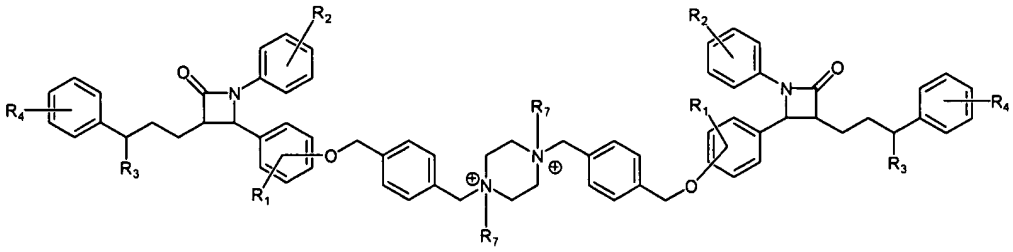


Scheme VIII illustrates the method utilized for the preparation of cholesterol absorption inhibitors of the type exemplified by structure **19**. The sequence commences by coupling

the aromatic iodide **14** with an appropriately substituted aryl or alkyl boronic acid by Suzuki reaction conditions. Conversion of the coupling product to the desired ammonium salts **19** was then accomplished by preparation of the corresponding aryl bromide or sulfonate ester derivatives followed by quaternization with an appropriate amine. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **19** wherein R_3 = OH.

[0083] Scheme IX

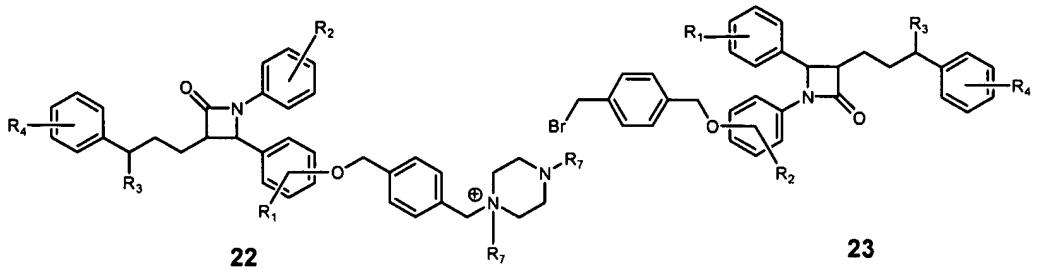




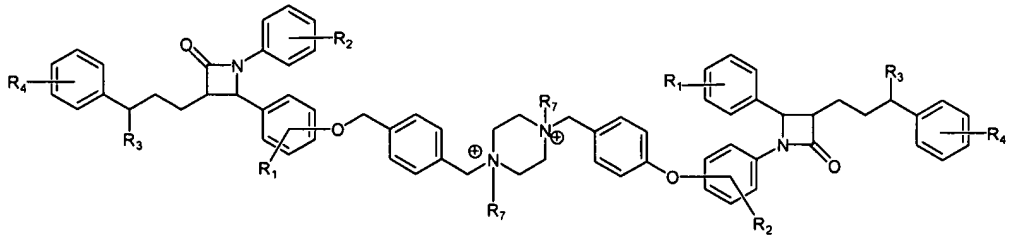
Illustrated in Scheme IX is the method that was employed to prepare compounds of the general formula **21**. The sequence commences with compound **1** or if desired the protected form **2** (from Scheme I) by treatment with α,α'-dibromo-*p*-xylene to afford the mono-bromo derivative **20**. Treatment of **20** with the quaternary ammonium salt **10** where in R_7, R_8 and R_9 are derived from an *N,N'* disubstituted piperazine derivative gave the desired *bis*-ammonium salts **21**. Deprotection of the benzylic TBS ether (if present)

then affords the desired cholesterol absorption inhibitors **21** wherein R_3 = OH.

[0084] Scheme X



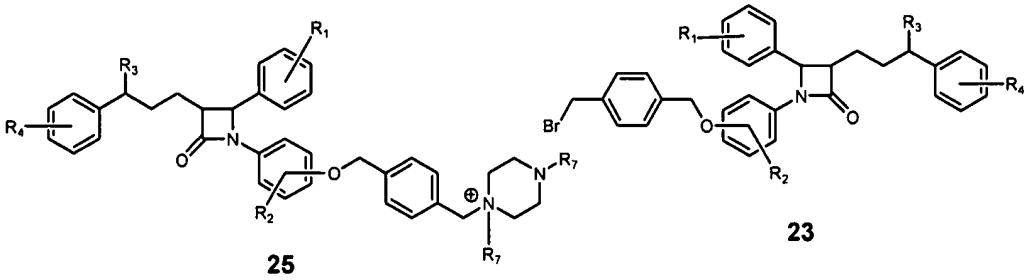
22 **23**



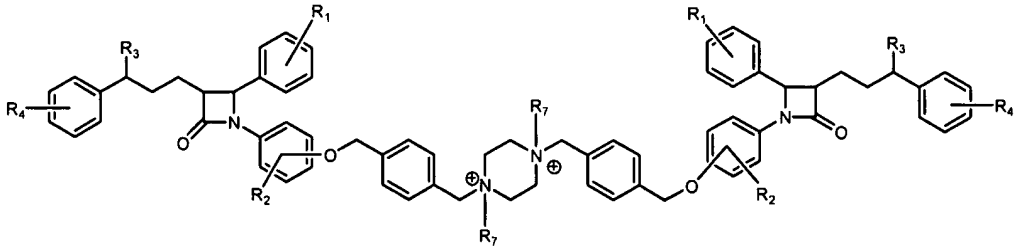
24

Illustrated in Scheme X is the general method that was used for the preparation of *bis*-ammonium salts of the general formula **24**. Treatment of α-bromoxylene derivatives (**20**) with an *N, N'* disubstituted piperazine derivative affords salts of the type **22**. Condensation of the salts **22** with α-bromoxylene derivatives of the type **23** (prepared from phenols **6** and α,α'-dibromo-*p*-xylene) provides the desired *bis*-salts **24**. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **24** wherein R_3 = OH.

[0085] Scheme XI



25 **23**



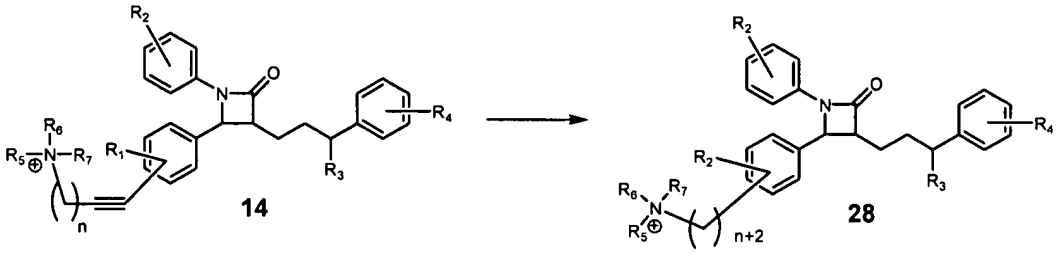
26

Illustrated in Scheme XI is the general method that was used for the preparation of *bis*-ammonium salts of the general formula **26**. Treatment of α-bromoxylene derivatives (**23**) with an *N, N'* disubstituted piperazine derivative affords salts of the type **25**. Condensation of the salts **25** with α-bromoxylene derivatives **23** provides the desired *bis*-salts **26**. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **26** wherein R_3 = OH.

[0086] Scheme XII

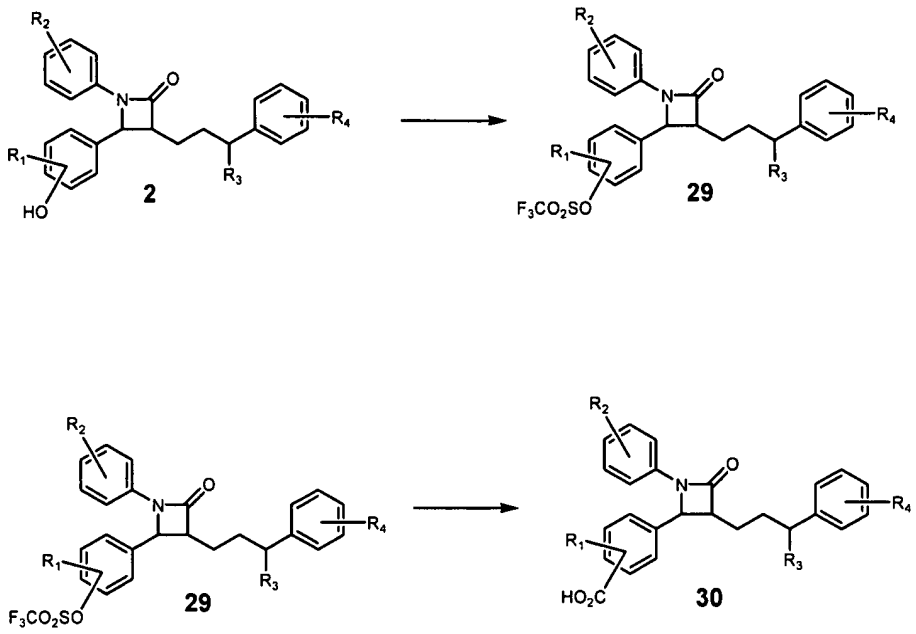
Illustrated in Scheme XII is the general method for the preparation of ammonium salts of the general formula **27**. The method for the preparation of these analogues is catalytic hydrogenation of the corresponding acetyleneic salts **13**. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **27** wherein R_3 = OH.

[0087] Scheme XIII



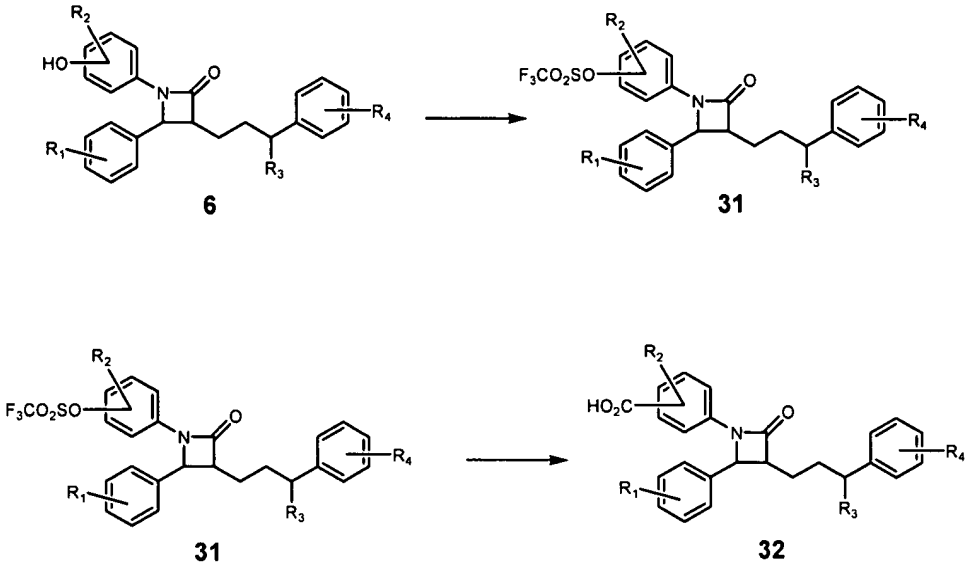
Illustrated in Scheme XII is the general method for the preparation of ammonium salts of the general formula **28**. The method for the preparation of these analogues is catalytic hydrogenation of the corresponding acetyleneic salts **14**. Deprotection of the benzylic TBS ether (if present) then affords the desired cholesterol absorption inhibitors **28** wherein R_3 = OH.

[0088] Scheme XIV



Illustrated in Scheme XIV is the general method that was employed for the preparation of carboxylic acids of the type exemplified by compound **30**. The sequence commences with the conversion of phenols of the general formula **2** to their corresponding trifluoromethane sulfonate esters **29** upon treatment with *N*-phenyltrifluoromethanesulfonimide in the presence of triethylamine. The triflate **29** is then converted into a carboxylic acid by dissolving in dimethyl sulfoxide and treatment with carbon monoxide in the presence of palladium II acetate and 1,1-bis-(diphenylphosphino)ferrocene (dppf). Deprotection of the benzylic TBS ether then affords the desired cholesterol absorption inhibitors **30** wherein R_3 = OH. The carboxylic acids of the type **30** are also useful intermediates for the preparation of cholesterol absorption inhibitors.

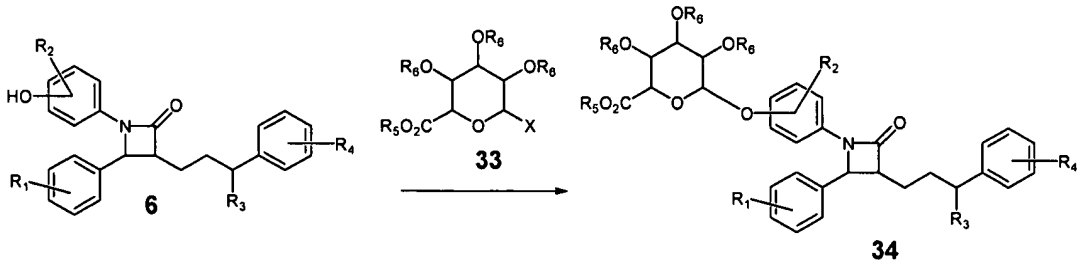
[0089] Scheme XV



Illustrated in Scheme XV is the general method that was employed for the preparation of carboxylic acids of the type exemplified by compound **32**. The sequence commences with the conversion of phenols of the general formula **2** to their corresponding trifluoromethane sulfonate esters **31** upon treatment with *N*-phenyltrifluoromethanesulfonimide in the presence of triethylamine. The triflate **31** is then converted into a carboxylic acid by dissolving in dimethyl sulfoxide and treatment with carbon monoxide in the presence of palladium II acetate and 1,1-bis-(diphenylphosphino)ferrocene (dppf). Deprotection of the benzylic TBS ether then affords the desired cholesterol absorption inhibitors **32** wherein R_3 = OH. The carboxylic acids of the type **32** are also useful intermediates for the preparation of cholesterol absorption inhibitors.

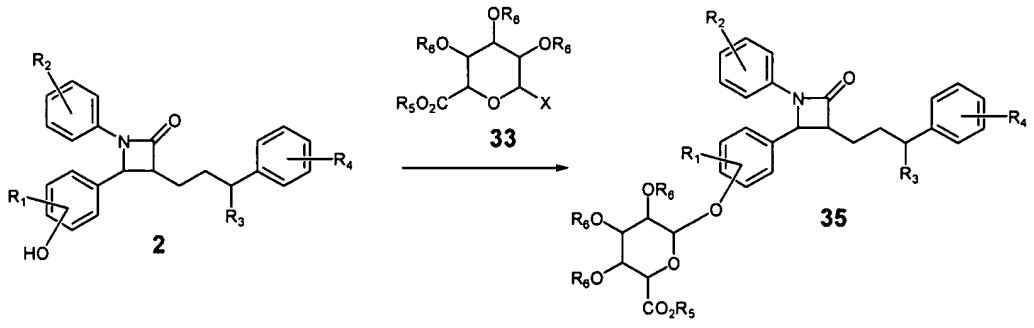
[0090] The trifluoromethane sulfonate esters **29** and **31** are also useful for the preparation of acetylene substituted cholesterol absorption inhibitors **13** and **15** by the Sonogoshira reaction. In addition, the Suzuki coupling method may employ **29** and **31** as coupling partners for the preparation of cholesterol absorption inhibitors **17** and **19**.

[0091] Scheme XVI



Illustrated in Scheme XVI is the general method for the preparation of cholesterol absorption inhibitors of the general formula **34**. The synthesis commences with the coupling of a donor phenol **6** with an activated sugar derivative **33** to effect coupling to afford the protected compounds **34**. The activating group may be, for example, -$OCNHCCl_3$. Subsequent deprotection, if desired, affords the cholesterol absorption compounds **34**. Reactions for adding and deprotecting sugars are described in US patent 5,756,470, which is incorporated herein by reference.

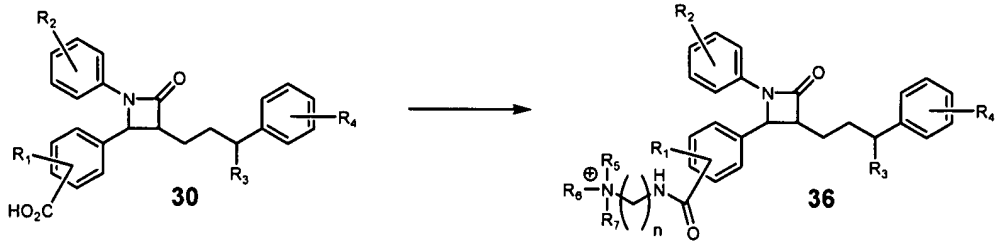
[0092] Scheme XVII



Illustrated in Scheme XVII is the general method for the preparation of cholesterol absorption inhibitors of the general formula **35**. The synthesis commences with the coupling of a donor phenol **2** with an activated sugar derivative **33** to effect coupling to afford the protected compounds **35**. Subsequent deprotection, if desired, affords the

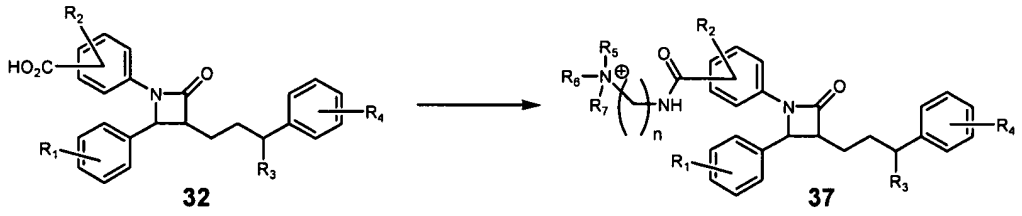
cholesterol absorption compounds **35**.

[0093] Scheme XVIII



Illustrated in Scheme XVIII is the general synthetic method for the preparation of cholesterol absorption inhibitors of the formula **36**. The method involves coupling of the carboxylic acids **30** with an amino substituted ammonium salt under amide forming conditions to afford the desired salts **36**. Alternatively, the acids **30** can be coupled with a tertiary amine containing primary amine followed by quaternization with an alkyl halide (R7) to afford the salts **36**.

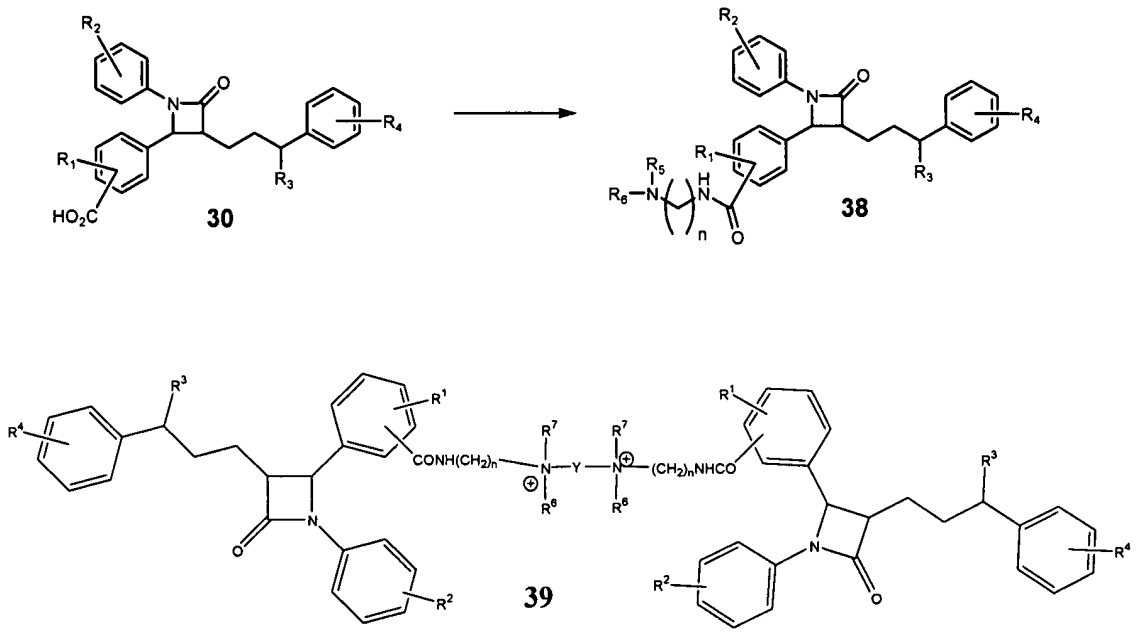
[0094] Scheme XIX



Illustrated in Scheme XIX is the general synthetic method for the preparation of cholesterol absorption inhibitors of the formula **37**. The method involves coupling of the carboxylic acids **32** with an amino substituted ammonium salt under amide forming conditions to afford the desired salts **37**. Alternatively, the acids **32** can be coupled with a

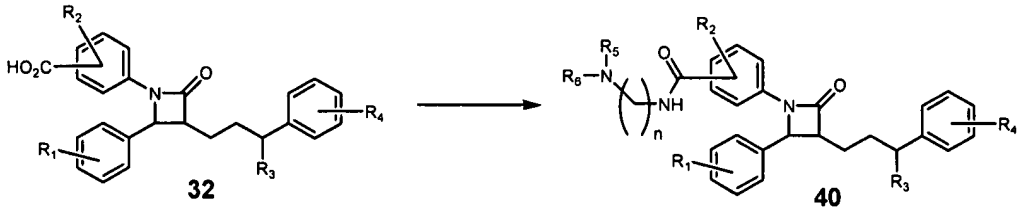
tertiary amine containing primary amine followed by quaternization with an alkyl halide (R7) to afford the salts **37**.

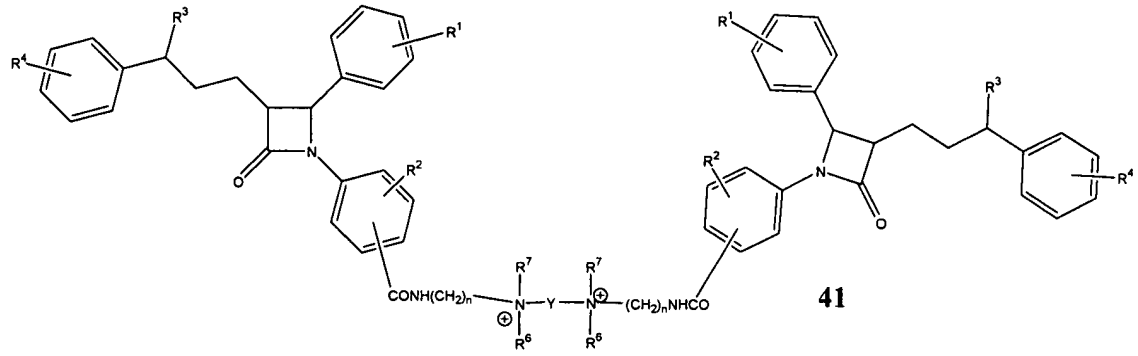
[0095] Scheme XX



Illustrated in Scheme XX is the general synthetic method for the preparation of cholesterol absorption inhibitors of the formula **39**. The method involves coupling of the carboxylic acids **30** with a tertiary amine containing primary amine followed by quaternization with a *bis*-alkyl halide (represented by the X in structure **39**) to afford the *bis*-salts **39**. Examples of *bis*-alkyl halides would be useful for the preparation of the *bis*-salts **39** would be compounds such as 1,4-dibromobutane, 1,3-dibromopropane, α,α'-dibromo-*para*-xylene, α,α'-dibromo-*meta*-xylene and the like.

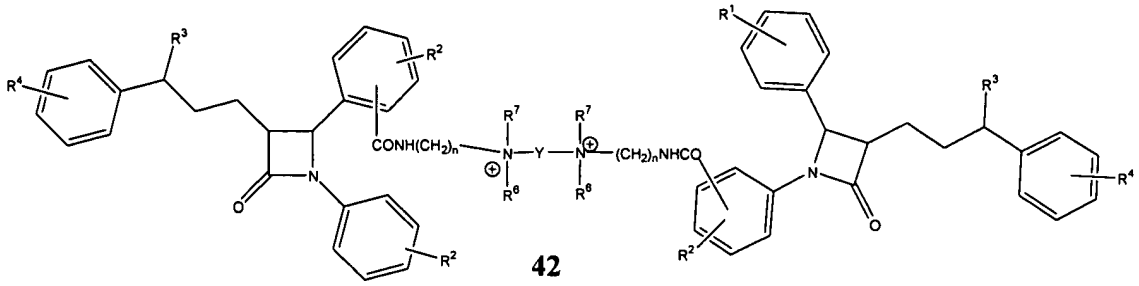
[0096] Scheme XXI





Illustrated in Scheme XXI is the general synthetic method for the preparation of cholesterol absorption inhibitors of the formula **41**. The method involves coupling of the carboxylic acids **32** with a tertiary amine containing primary amine followed by quaternization with a *bis*-alkyl halide (represented by the X in structure **41**) to afford the *bis*-salts **41**. Examples of *bis*-alkyl halides would be useful for the preparation of the *bis*-salts **41** would be compounds such as 1,4-dibromobutane, 1,3-dibromopropane, α,α'-dibromo-*para*-xylene, α,α'-dibromo-*meta*-xylene and the like.

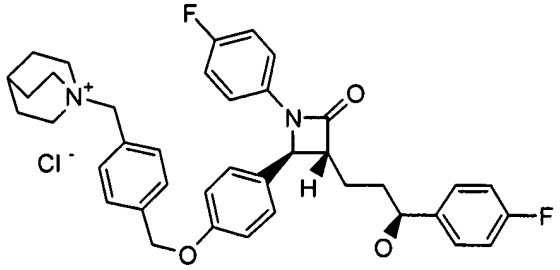
[0097] Scheme XXII



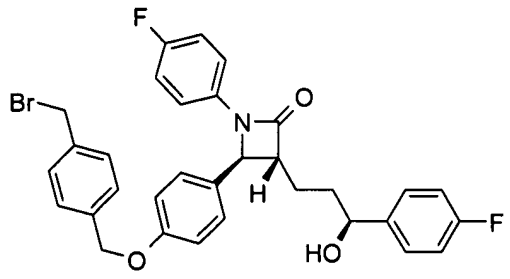
42

The compound illustrated in Scheme XXII as a *bis*-quaternary ammonium salt cholesterol absorption inhibitor, **42**. The preparation of **42** can be effected by treatment of a mixture of the tertiary amine containing derivatives **38** and **40** with a *bis*-alkyl halide. Examples of *bis*-alkyl halides would be useful for the preparation of the *bis*-salts **42** would be compounds such as 1,4-dibromobutane, 1,3-dibromopropane, α,α'-dibromo-*para*-xylene, α,α'-dibromo-*meta*-xylene and the like.

[0098] Preparation of 1-{4-[(4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)methyl]benzyl}-1-azoniabicyclo[2.2.2]octane chloride



[0099] Step 1. Preparation of (3R,4S)-4-[4-(4-bromomethyl benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one



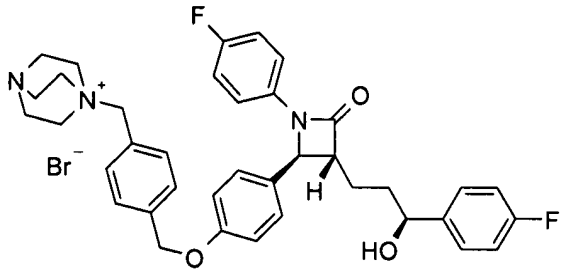
[00100] Cesium carbonate (344.7 mg, 1.06 mmol) was lightly flame-dried in a flame-dried flask. When cooled, N,N-dimethylformamide (DMF) (5.0 mL) was added via syringe followed by α,α'-dibromo-*p*-xylene (826.2 mg, 3.13 mmol) and finally (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one (254.1 mg, 0.621 mmol) both as solids. The reaction was stirred for 3 h at room temperature, diluted with ethyl acetate (20 mL), filtered through a pad of Celite® and washed with ethyl acetate (100 mL). The solution was transferred to a separatory funnel, washed with water (3 x 100 mL) and brine (50 mL), dried over sodium sulfate, filtered, concentrated and purified by chromatography (35 g silica gel, 10% to 90% ethyl acetate-hexane) to afford (3R,4S)-4-[4-(4-bromomethyl benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (265.3 mg, 72% yield) as a clear film.

[00101] Step 2. Preparation 1-{4-[(4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)methyl]benzyl}-1-azoniabicyclo[2.2.2]octane chloride

[00102] The product from Step 1 (138.6 mg, 0.234 mmol) was dissolved in dry acetonitrile (1.0 mL). Quinuclidine (26.0 mg, 0.234 mmol) in 1.0 mL of dry acetonitrile was added to the bromide mixture and the reaction was stirred at room temperature for 5 h. The solution was concentrated, purified by reverse-phase HPLC (21mm column, 35% to 65% acetonitrile-0.1% trifluoroacetic acid in water), passed through Dowex® 21K Cl (chloride) anion exchange resin in methanol and concentrated to afford 1-{4-[(4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-

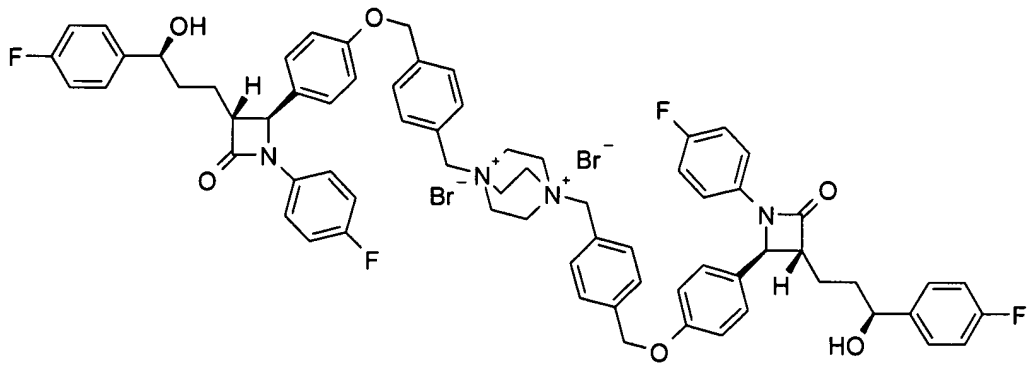
2-yl}phenoxy)methyl]benzyl}-1-azoniabicyclo[2.2.2]octane chloride (137.3 mg, 92% yield) as a glassy solid.

[00103] Preparation of 1-{4-[(4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)methyl]benzyl}-4-aza-1-azoniabicyclo[2.2.2]octane bromide



(3R,4S)-4-[4-(4-bromomethyl benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (55.9 mg, 0.094 mmol) was dissolved in dry acetonitrile (2.0 mL). A solution of 1,4-diazabicyclo[2.2.2]octane (9.5 mg, 0.085 mmol) in 0.5 mL of dry acetonitrile was added to the bromide mixture, the reaction was stirred at room temperature for 3 h and then concentrated. The residue was partitioned between water (30mL) and 1:1 ethyl acetate-hexane (30 mL), shaken to form an emulsion and transferred to two 50-mL Falcon® tubes. The samples were spun at 3000 rpm for 25 min and the aqueous layers are removed carefully via pipette, combined, concentrated at 35 °C and azeotropically dried with methanol (20 mL) to afford 1-{4-[(4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)methyl]benzyl}-4-aza-1-azoniabicyclo[2.2.2]octane bromide (54.8 mg, 92% yield) as a clear film.

[00104] Preparation of 1,4-bis{4-[(4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)methyl]benzyl}-1,4-diazoniabicyclo[2.2.2]octane dibromide



1-{4-[(4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)methyl]benzyl}-4-aza-1-azoniabicyclo[2.2.2]octane bromide (79.2 mg, 0.112 mmol) was dissolved in dry acetonitrile (1.0 mL). A solution of (3R,4S)-4-[4-(4-bromomethyl benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (74.2 mg, 0.125 mmol) in 2 x 3 mL of dry acetonitrile was added to the amine solution, the reaction was stirred at 50 °C for 3 h and then concentrated. The supernatant was decanted off and the remaining residue at the bottom of the flask was triturated with water (20 mL) and ethyl acetate (20 mL) and then azeotropically dried with methanol (20 mL) to afford 1,4-bis{4-[(4-{(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)methyl]benzyl}-1,4-diazoniabicyclo[2.2.2]octane dibromide (131.9 mg, 91% yield) as a clear glassy solid.